

# What history tells us XX. Felix Haurowitz (1896–1987) – A difficult journey in the political and scientific upheavals of the 20th century

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## 1. Introduction

Felix Haurowitz is mentioned in the historical accounts of 20th century biology as one of the authors of the instructive model of antibody synthesis, and one of its strongest and last supporters. He still argued in favour of this theory long after Frank MacFarlane Burnet had proposed the clonal selection theory at the end of the 1950s (Silverstein 1988; Moulin 1991; Fruton 1992).

By showing (or talking about) the highly different structures of the crystals of the oxy and deoxy forms of haemoglobin that he had obtained, he inspired Max Perutz to study haemoglobin – which led the latter to determine its three-dimensional structure and to receive the Nobel Prize for this accomplishment (Judson 1996). He was also the Professor of Jim Watson in Bloomington, Indiana, to whom he taught a model of protein synthesis in which nucleic acids had a non-specific role. They only supported the protein template involved in the reproduction of proteins (Olby 1974; Judson 1996).

He wrote many books, but in particular a famous one on proteins, *Chemistry and Biology of Proteins*, including more than 1500 references, the “Bible” of protein chemists (Haurowitz 1950).

Less well known is his difficult scientific career. He was obliged to abruptly leave the German University of Prague in 1939, and he spent ten years in Turkey before leaving for Bloomington (Putnam 1994).

What I would like to demonstrate is that the scientific successes and achievements, but also failures of Haurowitz cannot be disentangled from a scientific career profoundly perturbed by the ideologies and political events of the 20th century.

## 2. The template model of antibody formation

In 1930 Breinl and Haurowitz proposed for the first time the template model of antibody synthesis (Breinl and Haurowitz 1930). Both had been struck by the results obtained by Karl Landsteiner (whom Breinl had personally met), showing that any molecule synthesized by the chemist could be specifically recognized by antibodies produced by the organism. The old theory of the receptors of Ehrlich did not seem able to account for these astounding observations. The only reasonable hypothesis was that antigens actively participated in the formation of antibodies targeted against them.

Two similar models were proposed in the following months (Alexander 1931; Mudd 1932). But the way antigens “informed” antibodies was not clear. The structure of antibodies (and proteins in general) was progressively described in the 1930s, thanks in particular to new technologies such as ultra-centrifugation and electrophoresis. This allowed Linus Pauling to propose in 1940 a more precise model, in which the polypeptide chain of antibodies folded around the antigen molecule gave antibodies their precise conformation (Pauling 1940).

Less known is the fact that Pauling made huge efforts and succeeded in using this “natural mechanism” to generate antibodies *in vitro* with well-defined specificities (Pauling and Campbell 1942a, b; Kay 1989, 1993). The same principle was extended to the production of specific adsorbents (Dickey 1949). Haurowitz questioned the specificity of the reaction between some antigens and antibodies produced *in vitro* (Haurowitz *et al.* 1946). But he had no doubts about the value of the kind of models proposed by Pauling. In his influential book published in 1950 (Haurowitz 1950),

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he clearly distinguished two steps in the production of active, correctly folded proteins. The first is the positioning of amino acids at their right place in the polypeptide chain. In a second step, the long polypeptide folded and acquired its three-dimensional structure, by moulding on the antigens for antibodies, and by moulding on endogenous molecules, proteins, for other proteins and enzymes of the cells.

Since immunity can last decades, and as antibodies are unstable proteins, the only solution was to imagine that antigens remained present in organisms for years, a possibility that Burnet had put into question as early as 1941 (Burnet 1941).

From the 1930s, Haurowitz performed a lot of experiments to demonstrate their persistence, using radioactively labelled antigens when the latter became available (Hawkins and Haurowitz 1961), and to look for the site of antibody production.

From the end of the 1950s, many objections were raised to the instructive model of antibody formation. Burnet proposed the clonal selection theory, the molecular data demonstrated differences in the sequences of the immunoglobulin chains, and Jacques Monod showed that inducers did not have a stereospecific action on the structure of adaptive enzymes – during all these years, the synthesis of adaptive enzymes and specific antibodies had been considered as two similar examples of the direct action of the environment on the structure of proteins.

Haurowitz never renounced the idea that antigens play an active role in the formation of antibodies (Haurowitz 1960). In one of his last articles, in 1978, Haurowitz still considered the possibility that the antigen actively contributed to the assembly of the light and heavy chains of immunoglobulins (Haurowitz 1978).

Such perseverance is a sign of the difficulty of acknowledging that the apparent “perfect” specificity of antibodies is simply the result of chance variations – whatever their precise nature –, and natural selection of these variations.

### 3. Chemistry and biology of proteins

Most of the scientific work of Haurowitz was devoted to the study of the chemical structure of proteins. A first obligatory step was the preparation of pure proteins, and Haurowitz played an active part in the design of new protocols of purification. For its simplicity of purification, haemoglobin was one of his first and favoured objects of study. Not only did he crystallize the protein, and show the difference in structure between the oxy and deoxy forms (Haurowitz 1938), but he also characterized the nature of the link between the protein and the heme, and was the first to show the existence of a foetal form of haemoglobin, distinct from the adult one (Haurowitz 1935).

His major interest was the nature of the bonds stabilizing the structure of proteins. Although Emil Fischer, at the beginning of the 20th century, had proposed the “right” solution – proteins are long chains of amino acids uniquely linked by peptide bonds – it required a lot of effort to demonstrate the absence (in most cases) of other covalent bonds. The native structure of proteins is stabilized by weak bonds, to the characterization of which Haurowitz also devoted a lot of work.

Retrospectively, the study of protein structure is an atypical field of research (Tanford and Reynolds 2001). The right ideas were produced very early (*circa* 1900), but sixty years were necessary to obtain the first precise three-dimensional structures, and to confirm these early hypotheses. Many obstacles had to be painfully overcome: the abandonment of the colloid theory, the demonstration of the non-existence of covalent bonds except for the peptide one, the demonstration of the absence of folding rules for proteins.

It was an interdisciplinary field, in which chemists, physical chemists, physicists and biologists worked together. It was difficult for a single person to master the different approaches: the complex organic reactions used to characterize proteins and their amino acids, the sophisticated equations of thermodynamics, and the highly complex ways to relate the information provided by new technologies such as ultra-centrifugation to the structure of proteins.

The relations between these different specialist subjects were not perfectly balanced. The explanations of biological phenomena had to obey the results obtained by chemists. This explains why the role of nucleic acids was minimized. Since the chemical specificity of nucleic acids had apparently been shown to be limited, and there were fewer nucleotides than amino acids, this meant that nucleic acids had only a minor role in protein synthesis. The numerous biological observations showing the correlation between the presence of RNA and protein synthesis had to be interpreted within the framework derived from the chemical evidence.

The clarity and simplicity of Haurowitz’s book, and the cautious way he was able to embrace such a wide domain of research, were unanimously praised (Haurowitz 1950). But Haurowitz personally was a protein chemist (Haurowitz 1979), and he worked within the “protein paradigm” (Kay 1993). He “moulded” his biological models – on protein and antibody synthesis – on the evidence from chemistry. He was not a physical chemist. And despite a good knowledge of the field, and his use of osmometric methods and radioactive molecules, he never personally adopted sophisticated physico-chemical technologies, such as X-ray diffraction. Maybe the explanation of this strategic error has to be sought elsewhere, in the difficult academic career he had.

Personally, Felix Haurowitz was very cautious, and accumulated observations, convinced of the complexity

of biological phenomena (Haurowitz 1979). This attitude was at odds with the drastic simplifications introduced at the same time by molecular biologists such as Francis Crick.

#### 4. Felix Haurowitz in his century

Felix Haurowitz was the product of centuries of European (German) intellectual culture. The first fifteen years of his career were spent at the German University of Prague, a “remnant” of the Austrian political and cultural empire. He was Jewish, but agnostic. He baptized his children and, at home, the only feasts celebrated were Christian ones. His children were surprised when, in Turkey, they learnt that they were Jewish; an experience similar to that of Madeleine Albright, whose family was also from Prague (Reisman 2006).

The situation of Haurowitz dramatically changed in 1938 after the invasion of the Sudetenland by German troops, the adoption of Nazi rules by the German University of Prague, and his dismissal. He succeeded in leaving Czechoslovakia two weeks after the invasion of the country, and reached Istanbul, where he was appointed as Professor at the University.

The role that Turkey played in receiving Jewish academics abruptly dismissed from their universities, and sometimes even in extracting them from concentration camps, has recently been described (Widmann 2006). For the Turkish government, faithful to the policy of modernization initiated by Kemal Atatürk, these recruitments were an extraordinary opportunity to increase the standards and quality of its universities. More than 300 academics were recruited for a limited period of time. They had to teach large audiences of students in Turkish, and to develop research. Haurowitz respected this contract, and only left when it ended. After two years, he was able to lecture in Turkish, and he published a book on biochemistry in this language. He trained a generation of Turkish biologists and doctors, some of whom later emigrated to the United States.

For refugees like Haurowitz, the situation was only temporary. His personal hope was to return to a European university at the end of the war. Haurowitz’s children attended an English school. After the war, their mother took them to the United States, which decided Haurowitz to look for a position there, which he finally obtained in 1949.

Scientifically, the exile to Istanbul was felt by Haurowitz to be a catastrophe. He was well known in Europe, and the years 1938–1939 were scientifically the most productive for him. Suddenly, he had to interrupt his research, and to spend a lot of time teaching in a foreign language, and reinitiating research in difficult conditions, with huge difficulties in keeping in touch with the scientific community. He published many papers during his sojourn in Turkey, but he

favoured studies requiring unsophisticated and inexpensive materials, such as immunochemical experiments. His writing of *Chemistry and Biology of Proteins* was probably the consequence of this forced partial inactivity in research. One can imagine that, in other conditions, Haurowitz would not have left aside his observations on haemoglobin crystals, and would have developed the sophisticated technologies necessary to pursue these observations.

More profoundly, his expulsion from the University of Prague, the difficulties he faced after the war in obtaining a position in the United States, were a terrible blow to his self-esteem. Maybe his delayed attachment to the instructive model of antibody formation was a way to remain close to what had made him famous, and to re-establish a continuity in his scientific career interrupted by the war.

Historiography has not been fair to refugees like Haurowitz. Whereas German Jewish refugees, intellectuals, scientists, have received a lot of attention from historians (Fleming and Baylin 1969; Nachmansohn 1979), the same is not true for refugees from other European countries. In the renewed political landscape of Europe after the war, people like Haurowitz had no place: he was neither German, nor Czech. Even the Hungarian refugees received more attention (Hargittai 2006), thanks maybe to their contribution to the atomic bomb! Protein chemistry had not the same visibility.

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